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TEACHERS' TOPICS

The Chemically Elegant Proton Pump Inhibitors

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Medicinal chemistry instruction at Creighton University is designed to provide an in-depth scientifically grounded and clinically relevant learning experience for pharmacy students. Each topic covered in the 2-semester required course sequence is selected based on the general utility of the compounds in question and/or the therapeutic importance of the drugs in treating life-threatening diseases. All lessons provided to campus- and Web-based students by the author are in the form of a descriptive and conversational narrative and course requirements are in place to assure that students read the lesson prior to the class period in which it is discussed. Learning tools and aids are provided to help students more readily discern the most critical aspects of each lesson, to practice required critical thinking and structure analysis skills, and to self-assess competency in meeting specific learning objectives. This manuscript illustrates this approach by sharing a lesson on the chemistry and clinically relevant structure-activity relationships of proton pump inhibitors.

Keywords: medicinal chemistry, proton pump inhibitors, gastroesophageal reflux disease, ulcer

INTRODUCTION

At Creighton University, medicinal chemistry is offered to second-year pharmacy students through a 5-credit hour experience that spans both semesters of the academic year.[1] The courses, entitled *Chemical Basis of Drug Action I* and *II*, are required of both campus- and Web-based students and are structured around an articulated set of learning objectives, guiding principles, and teaching philosophies that are explicitly shared with the students. Students enrolled in the *Chemical Basis* courses are concurrently enrolled in 10 credit hours of *Pharmacology* coursework and have successfully completed classes in general, organic, and biochemistry as well as physiology and pathology. While the chemistry and pharmacology courses are not formally integrated, the *Chemical Basis* instructors do their best to link their content to that already presented in pharmacology whenever possible. Four class periods at the beginning of the fall course are devoted to a focused review of acid-base chemistry, functional group chemistry and drug receptor structure and common binding interactions. Another 3 lessons that provide an in-depth structure-based discussion of drug metabolism are covered before the chemical dissection and analysis of specific classes of therapeutic agents begin.

A practice-oriented approach that emphasizes the relevance of chemistry to the contemporary practice of pharmacy has long been a hallmark of the *Chemical Basis* courses.[2-5] Students have specifically stated verbally and in writing that they take what they have learned about drug chemistry into the workplace when they evaluate therapies and/or interact with patients (Appendix 1). The courses are purposefully organized to move from the more simplistic to the more mechanistically complex structures since students' confidence and competence in analyzing drug structures and translating them into pharmacologic action and therapeutic utility can only come with time, practice, and initial success in higher-order thinking skills. However, the proton pump inhibitors are an exception to this usual topic layout as they are covered in the fall semester course as part of a 2-lesson series on anti-ulcer agents. This series also includes the relatively simple H2 antagonists, which are purposefully covered immediately after a discussion of the H1-antihistamines (also a chemically straightforward lesson). The anti-ulcer lessons come toward the end of the fall term when most students have grasped the steps inherent in structure analysis and have found their "rhythm" with the requirements and intellectual expectations of *Chemical Basis* lessons. Nevertheless, proton pump inhibitor chemistry is the most mechanistically intricate of the compounds they have studied. Understanding and appreciating the elegance inherent in the chemical design of these highly popular

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drugs necessitates a step-by-step "guided tour" of the chemical choreography that converts these "prodrug" structures into reactive disulfide-forming enzyme destroyers.

CHEMICAL BASIS LESSONS

The format of the *Chemical Basis* lessons prepared by the author has been previously described[1] and is briefly summarized here. Each topic is delivered to students as a conversational self-explanatory lesson handout organized to provide the following:

- a brief introduction to the topic
- pertinent review (eg, biochemical pathways impacted by the drugs under study and the pharmacological mechanism of action)
- the chemical nature of the binding site
- drug-receptor binding graphics
- a receptor-based discussion of the pharmacophore
- structure activity relationships (SAR)
- pathways of metabolic activation/inactivation
- therapeutic agents and clinical correlates

"Brain Teaser" questions are utilized sparingly throughout the lessons to stimulate thinking and keep students engaged in the content.

Specific learning objectives for each lesson are provided via the course website, as is a summary of the most important concepts or "take home" messages (entitled "Med Chem To Go"). Students read these documents and the lesson handout prior to the class period in which the material will be formally presented and take an online open-book quiz on the key concepts and SAR discussed in the lesson handout. To reward students for proactive preparation for an engaged and advanced class discussion, the quiz average counts for 10% of each student's final course grade. Optional (but strongly encouraged) application exercises are made available to give students additional practice with the skills and abilities they will be expected to demonstrate on examinations. These optional exercises take the form of structure challenge exercises, study questions, problem worksheets, case studies, and practice examinations. Faculty members encourage students to share their answers to these optional exercises with the faculty member so they can benefit from a one-on-one consultation on performance strengths and weaknesses.

The handout constructed for the proton pump inhibitors lesson is provided below. The handout is not referenced but students are made aware that lesson material comes from information found in widely utilized medicinal chemistry textbooks and from the scientific and clinical literature.[6-14] The learning objectives and study questions that were constructed for this lesson are provided as Appendix 2 and 3, respectively.

PROTON PUMP INHIBITOR LESSON

Introduction

No matter what the source of gastric acid secretion stimulation (histamine gastrin or acetylcholine) the only way acid gets from parietal cell to the lumen of the stomach is by the action of the enzyme H^+, K^+-ATPase also known as the proton pump. This pump is located in the *canaliculus* (the acid-secreting network of the parietal cell) and is stimulated to secrete acid by the cyclic adenosine monophosphate, produced through action of histamine on the Gs coupled H2 receptor. Ca^{+2} can also stimulate acid secretion and intracellular concentrations of this ion are increased when gastrin and ACh act on their receptors.

When H2 antagonists are administered, histamine is unable to stimulate the proton pump to release hydrochloric acid into the stomach. However, gastrin and ACh are still actively at work. In order to stop the secretion of all gastric acid, regardless of the original chemical stimulus, you must inhibit the pump itself because it is the very last step in the acid secretion process.

In addition to stopping acid stimulated by the mediators mentioned above, proton pump inhibitors (PPIs) also stop the basal secretion of gastric acid, making them very comprehensive and potent therapeutic agents in the treatment of gastroesophageal reflux disease (GERD) and gastric or duodenal ulcer. Daily esophageal reflux occurs in approximately 4%-7% of the US population, with approximately 2% suffering esophageal erosion secondary to acid reflux. While H2 antagonists might be sufficient in managing the symptoms of mild GERD, studies have shown superior esophageal healing with the use of PPIs, and they are the agents of choice in moderate-severe disease. In 2003, 80% of family physicians prescribed a PPI to treat patients with GERD.

Because PPIs stop gastrin-mediated acid secretion, gastrin secretion increases, leading to hypergastrinemia. The excessively high gastrin levels can lead to hyperplasia of the histamine-containing ECL cells of the gastric fundus. Fortunately, progression of this hyperplasia to carcinoid tumors has not been noted in humans.

Proton Pump Chemistry

The H^+, K^+ ATPase proton pump is a large protein comprised of 2 subunits; the catalytic alpha subunit and a glycosylated regulatory beta subunit. The alpha subunit has 10 transmembrane- or membrane-inserted segments and contains a total of 28 cysteine (CYS) residues. CYS813 has been identified as the residue most critical to the inhibiting action of the PPIs. This CYS is located in the luminal vestibule of the ATPase and is accessible from the extracytoplasmic area of the ATPase protein.

CYS813 will interact with all activated PPI structures regardless of their chemical reactivity. PPIs that are more slowly activated also have time to react with CYS822.

Unlike H2 antagonist compounds that interact competitively and reversibly with the H2 receptor, PPIs form a covalent disulfide bond with the ATPase enzyme, leading to an irreversible inhibition of the pump. One sulfur atom in the disulfide bond will come from a CYS residue on the ATPase and the other will come from the PPI. Since the inactivation of the receptor site (the ATPase in this case) is irreversible and complete, the PPIs are very potent and long-acting therapeutic entities. The ATPase is not able to recover from its irreversible interaction with the inhibitor structure (the disulfide bond formed is non-reducible) and the body must synthesize new enzyme de novo which takes time. Until new protein is made, gastric acid secretion is halted.

In addition to CYS813 and CYS822, an anionic GLU820 and a second anionic residue (GLU or ASP) at position 824 are believed to be important in holding the PPI structure to the enzyme and positioning the drug for irreversible interaction with the CYS residue.

Proton Pump Inhibitor Chemistry

The PPI pharmacophore is 2-pyridylmethylsulfinylbenzimidazole (Figure 1). The 5 PPI products currently on the market (omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole) all contain this basic structural framework and differ only in the nature of substituents placed on the pyridine and benzimidazole rings. We will soon see that the electron donating or withdrawing nature of these substituents has a significant impact on chemical reactivity and onset of antisecretory action.

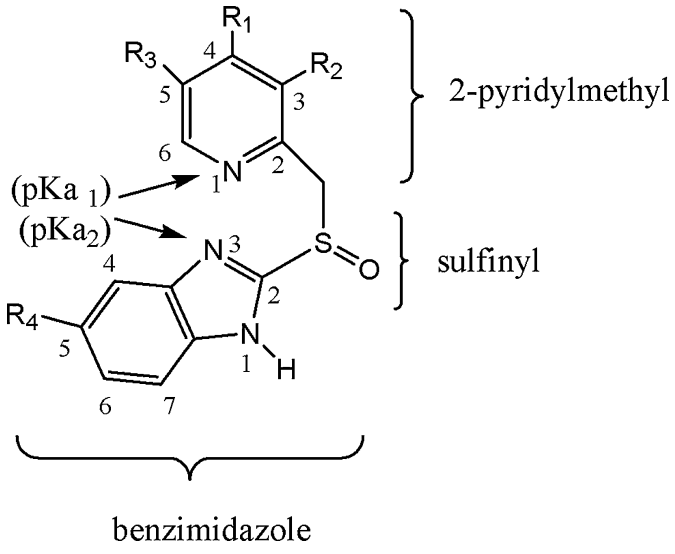

Figure 1. The 2-pyridylmethylsulfinylbenzimidazole proton pump inhibitor pharmacophore with pKa_1 and pKa_2 sites identified.

The sulfinyl moiety found in the parent PPI structures is not sufficiently reactive to form the essential disulfide bond with the proton pump CYS residues and must first be activated through 2 protonations and a subsequent spontaneous rearrangement to form the active sulfenamide or sulfenic acid derivatives. The need for activation means that the PPIs are inactive as administered. Sometimes they are referred to as "prodrugs" but this is somewhat of a misnomer since they do not require enzymatic activation. The entire PPI activation scheme is shown in Figure 2. Let us take a closer look at these critical reactions in order to understand how the PPIs really work.

Remember that the PPI activation pathway begins with 2 protonation reactions which occur readily in the highly acidic parietal cell. Your knowledge of acid-base chemistry should tell you that only 2 of the PPI's 3 nitrogen atoms are capable of accepting proton: the pyridine nitrogen and the doubly bonded benzimidazole nitrogen (N3).

The pKa of the pyridine nitrogen (referred to as the pKa1) runs between 3.83 (lansoprazole and pantoprazole) and 4.53 (rabeprazole). The first marketed PPI,

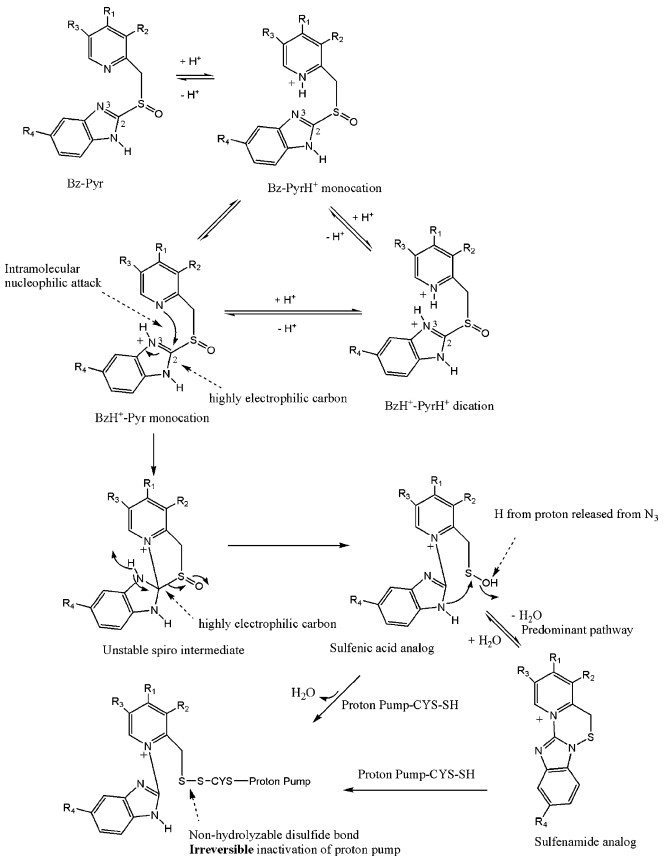

Figure 2. The proton pump inhibitor activation and reaction pathway.

omeprazole (and its pure S-isomer esomeprazole), has a pKa1 of 4.06. These pKa1 values ensure that the pyridine nitrogen of all PPIs will be almost completely cationic at the low pH (1.3) of the parietal cells, thus trapping the drug right at the site of action. Prove it to yourself with the Henderson-Hasselbalch equation! Go on. . ..do it!

While the highly cationic nature of the pyridine nitrogen is helpful in trapping the PPI in the parietal cells (the site of action), it will be the unionized conjugate (BzH^+-Pyr, see Figure 2) that generates the activated form of the PPIs by conducting an intramolecular nucleophilic attack at the C2 position of the benzimidazole. Even though there will be very little of the nucleophilic unionized pyridine conjugate available, it will be absolutely critical to the ability of the PPIs to irreversibly inhibit the proton pump. More on that in a minute!

Electron donating substituents on the pyridine ring (especially at the R1 position) will push electrons to the pyridine nitrogen and increase the percentage existing in cationic form at gastric pH. However (and more importantly), this electronic enrichment will also increase the nucleophilic character of any PPI pyridine nitrogen atoms in the unionized conjugate base form. For this reason electron donating substitutents on the pyridine ring enhance the rate of formation of the active sulfenic acid/ sulfenamide rearrangement products. Electron withdrawing substituents would of course have the opposite effect.

The pKa value of the benzimidazole N3 (designated as pKa2) is much lower than that of the pyridine nitrogen and ranges from 0.11 (pantoprazole) to 0.79 (omeprazole and esomeprazole). Lansoprazole and rabeprazole have identical pKa2 values of 0.62. These lower pKa values mean that the benzimidazole ring protonates after the pyridine ring and the extent of protonation will be significantly lower. None-the-less the higher the pKa2 value the more willingly the benzimidazole nitrogen accepts proton and becomes cationic.

A cationic benzimidazole N3 (as found in BzH^+-$PyrH^+$ and BzH^+-Pyr, see Figure 2) is critical to the activation of the PPIs since it will pull electrons through σ bonds from the adjacent benzimidazole C2, rendering it highly electron deficient. As mentioned the benzimidazole C2 will be attacked by the unionized pyridine nitrogen and the more electrophilic (δ^+) it is the faster the attack will be. Since this intramolecular nucleophilic attack generates the active form of the PPI, the rate at which it occurs will determine the rate at which the proton pump will be inactivated.

Electron donating substituents on the C5 position of the benzimidazole ring will push electrons to N3 and increase the percentage existing in cationic form at gastric pH. This in turn increases the electrophilic character of adjacent C2 due to negative induction (loss of electron density from C2 to the cationic nitrogen). For this reason electron-donating substitutents on the benzimidazole ring enhance the rate of formation of the active sulfenic acid/ sulfenamide rearrangement products (Table 1).

Once the benzimidazole N3 is protonated, an equilibrium is established between the dication (BzH^+-$PyrH^+$ with both the benzimidazole and pyridine nitrogens protonated) and the 2 monocations (BzH^+-Pyr and Bz-Pyr H^+). Only the BzH^+-Pyr monocation, which has the unionized pyridine nitrogen, is capable of conducting the intramolecular nucleophilic attack at C2 to produce the active sulfenamide/sulfenic acid products. Only a few molecules of this essential monocation will be available at any given time. Once the intramolecular nucleophilic attack occurs and the reactive sulfenamide/sulfenic acid species are generated, the acid-base equilibrium will shift to provide additional unionized pyridine monocation molecules. Eventually all (or most) of the PPI molecules will be activated and form disulfide bonds with the vulnerable proton pump CYS residues.

Now let us look at that all-important intramolecular nucleophilic attack. The lone pair of electrons of the unionized pyridine nitrogen attacks at the C2 of the benzimidazole ring, a position made highly electrophilic by protonation of the adjacent N3. When the pyridine attacks, a new bond is formed between the benzimidazole carbon and the pyridine nitrogen. When you make a new bond, you must break an old bond and the bond that breaks is the bond between the benzimidazole nitrogen and the sulfinyl sulfur atom. Note that a new 5-member ring has formed. This new intermediate is called a *spiro* compound because 2 rings are now joined at a single quaternary carbon (this nomenclature should be familiar from "spironolactone"). Note also that the benzimidazole is now partially reduced (only 1 double bond remains).

Now another "make-a-bond-break-a-bond" sequence occurs. The spiro carbon is highly electron deficient because it is surrounded in all directions by strongly electron-withdrawing atoms or groups (especially the cationic nitrogen atom and the sulfinyl). It is literally screaming for electrons. To satisfy this demand, electrons from the N3-H bond are donated to this carbon, thereby regenerating the "lost" benzimidazole double bond and releasing

Table 1. pKa Values of Marketed Proton Pump Inhibitors

Proton Pump Inhibitor	pKa1	pKa2
Omeprazole/esomeprazole	4.06	0.79
Lansoprazole	3.83	0.62
Pantoprazole	3.83	0.11
Rabeprazole	4.53	0.62

the N3-hydrogen as proton. When this double bond forms, it forces the bond between the benzimidazole and the sulfinyl sulfur atom to break. The oxygen atom of the sulfinyl group willingly takes the released proton, converting the sulfinyl to sulfenic acid (R-S-OH). The sulfenic acid moiety can form a disulfide bond with the sulfhydryl (SH) group of proton pump CYS813 or CYS822 residues, releasing a molecule of water in the process.

More commonly, however, the lone pair of electrons on the pyrrole-type nitrogen of the benzimidazole attacks the electron deficient sulfur atom of the sulfenic acid to generate a cyclic thiadiazine structure known as a sulfenamide. Again, a molecule of water is lost in the process. The sulfenamide sulfur atom is electron deficient because of its proximity to so many electron-withdrawing nitrogen atoms. This electron-deficient sulfur is equally capable of forming a disulfide bond with the nucleophilic SH group on the critical proton pump CYS residues. When it does, the thiadiazine ring breaks and the proton-pump adduct that forms is identical to that formed by the sulfenic acid product.

Regardless of how it forms, the disulfide bond between the proton pump and the PPI is extremely stable and non-reducible. That means that the disulfide bond cannot break to regenerate the free SH group on the proton pump CYS residues. The inhibition is therefore irreversible. This molecule of H^+,K^+-ATPase is dead and will no longer secrete acid in response to anything (ACh gastrin histamine. . .anything!).

It should be noted that the sulfur atom on both the sulfenamide and the sulfenic acid analog is perfectly positioned to accept the attacking CYS-SH because the molecule is being held in place by bonds formed between the PPI and the 2 anionic proton pump residues found at positions 820 (GLU) and 824 (either GLU or ASP).

Brain Teaser: Since the site of action of PPIs is the *gastric* parietal cell, why are all PPI products marketed as enteric coated (delayed release) tablets or capsules?

This Brain Teaser is a tough one, so I'm going to help you out. To reach CYS813 and/or CYS822, the proton pump inhibitor structure must interact with the ATPase in the area of the luminal vestibule. To reach this site intact the drug must be systemically absorbed and then distribute back into the stomach (in its unionized form) from the general circulation. If the PPI structures encountered gastric acid in the stomach lumen immediately after oral administration, they would be activated too soon and would react non-selectively with CYS residues found on proteins in the stomach lining. However, when protected by enteric coating, the drug will not be released from the formulation until it reaches the intestine. The higher pH of intestinal fluid (5.5) and blood (7.4) ensures that the pyridine and benzimidazole nitrogens of the PPI remain unionized while the inhibitor molecule makes its way back to the stomach. Once it diffuses back from the general circulation across the gastric membranes (eg, comes in through the "back door") it encounters the acid-filled canalicular network, protonates, rearranges and zaps the CYS residues of the proton pump.

Proton Pump Inhibitor Metabolism

(Did you really think I was going to let you get away without this important discussion?) Proton pump inhibitors bind strongly to serum proteins and are extensively metabolized by the CYP450 family of enzymes. The 2C19 isoform is particularly important in converting parent structures to inactive metabolites, although CYP3A4 also plays a role in PPI biotransformation. Some agents, most notably omeprazole (and its pure S isomer esomeprazole) and are not only metabolized by CYP isoforms. . .they inhibit them, too. Both CYP2C19 and CYP2C8 are inhibited by these PPIs. This of course leads to the potential for significant drug-drug interactions. Fortunately, despite the hypothetical risk, few metabolism-based drug-drug interactions involving the PPIs are of clinical significance.

The metabolic degradation pathways of the currently marketed PPIs are provided in Figures 3–6. A significant fraction of the dose is biotransformed in the gut and via first-pass metabolism. In addition to the oxidative metabolites generated by CYP450 isoforms, the sulfinyl group can be non-enzymatically reduced to the sulfide (also called a *thioether*).

Omeprazole, esomeprazole, pantoprazole, and lansoprazole undergo extensive CYP-mediated metabolism. While the metabolic pathway of enantiomerically pure esomeprazole mimics its racemate omeprazole, it has a lower dependency on CYP2C19-mediated metabolism and a greater reliance on CYP3A4-catalyzed biotransformation. Still, CYP2C19 is the major isoform involved in the metabolism of both omeprazole and esomeprazole although esomeprazole is metabolized at only one third the rate of the R isomer. In contrast, CYP plays a relatively minor role in rabeprazaole metabolism. As a result this PPI has the lowest risk of drug-drug interactions (other than those that result from its antisecretory action).

Patients who do not express CYP2C19 (poor 2C19 metabolizers) will achieve a greater response from CYP2C19-vulnerable PPIs (essentially all PPIs except rabeprazole). Poor CYP2C19-metabolizing phenotypes are prevalent in people of Chinese (14.3%), Korean (14.0%), or Japanese (21.3%) descent. Although other proton pump inhibitors are also metabolized by

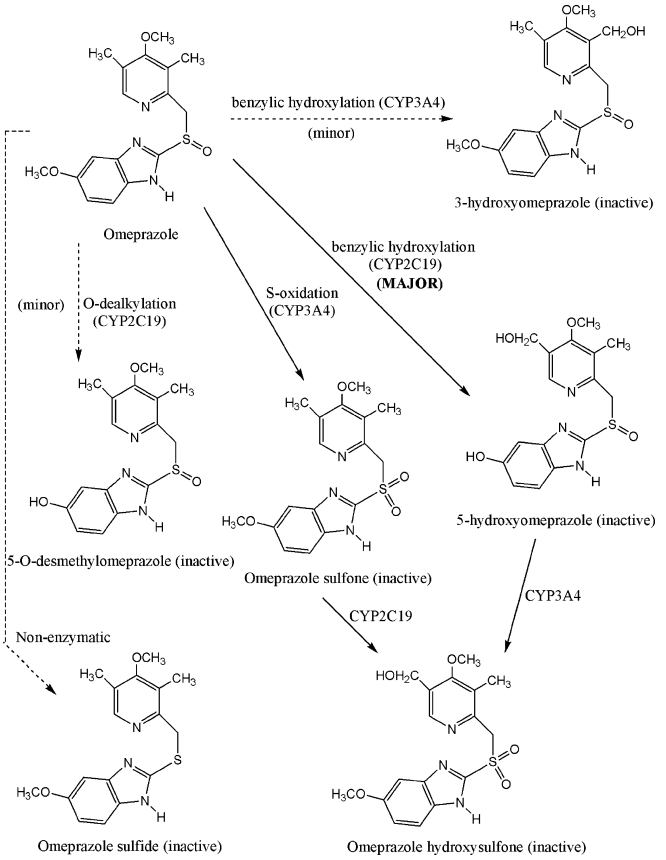

Figure 3. Omeprazole/Esomeprazole metabolism.

CYP2C19, the greatest risk for toxicity occurs with omeprazole and esomeprazole because these agents most actively inhibit this isoform. Extensive 2C19 metabolizers may present as "non-responders" to normal therapeutic doses of all PPIs except rabeprazole, which works equally well in all patients despite CYP2C19 phenotype.

Drug-Drug Interactions Due to Proton Pump Inibitor-Induced Achlorhydria

While PPIs are relatively safe drugs in and of themselves, dosages may need to be decreased in patients with severe hepatic impairment or in the elderly. However, since proton pump inhibitors are designed to induce achlorhydria (lack of gastric acid) this can interfere with the absorption of some co-administered drugs. Drug-drug interactions between proton pump inhibitors and the following drugs have been identified or are strongly suspected:

- cephalosporin antibiotics (decreased absorption)
- clarithromycin (increased absorption)
- digoxin (increased absorption)
- ketoconazole (decreased tablet dissolution leading to decreased absorption)

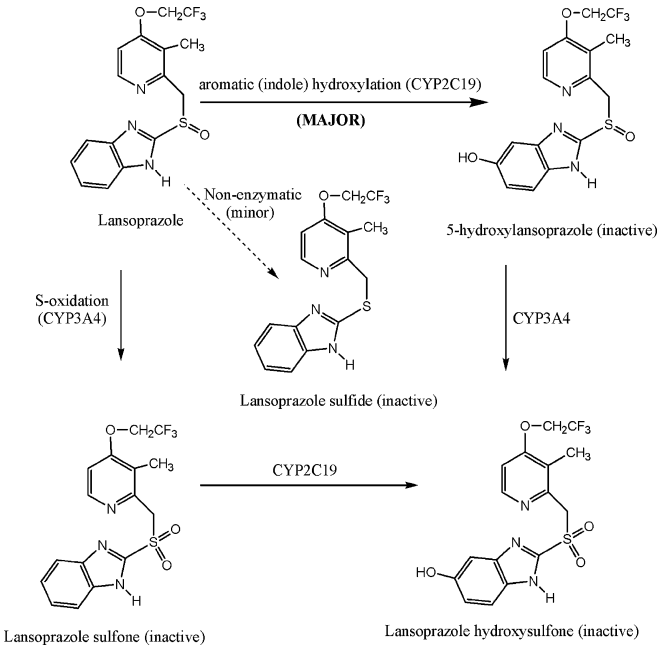

Figure 4. Lansoprazole metabolism.

- indinavir (decreased tablet dissolution leading to decreased absorption)
- salicylates (increased enteric-coated tablet dissolution leading to an increase in gastric side effects)
- theophylline (increased absorption from sustained release formulations)
- vitamin B12 (decreased absorption)

Proton Pump Inhibitor Products

Omeprazole (Prilosec) and Esomeprazole Magnesium (Nexium). Indications include active duodenal ulcer, gastric ulcer, GERD, erosive esophagitis, and

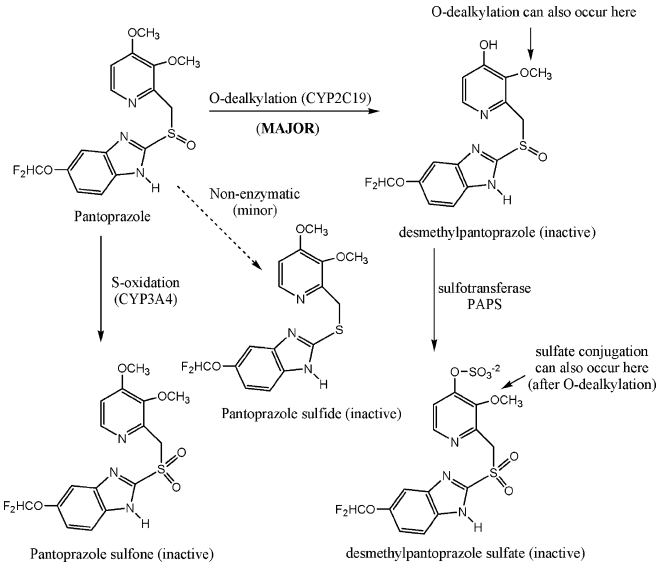

Figure 5. Pantoprazole metabolism.

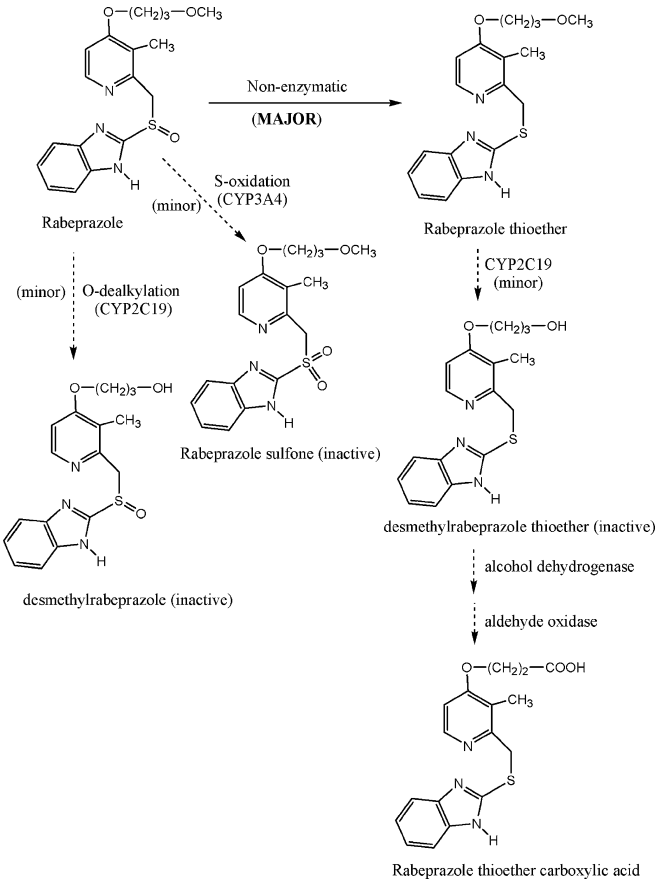

Figure 6. Rabeprazole metabolism.

hypersecretory conditions. Dosage Forms: omeprazole: capsules (20 mg, 40 mg, and 10 mg delayed release), tablets (20 mg delayed release, 20 mg powder for oral suspension); Esomeprazole: capsules (20 mg and 40 mg delayed release), powder for intravenous injection (20 mg and 40 mg).

SAR Notes. The methoxy group at position 4 of the pyridine ring donates electrons through resonance to the pyridine nitrogen. This not only increases the percentage of cationic pyridine (which sequesters the drug at the site of action), it also increases the nucleophilic character of any molecules of the PPI with an unionized pyridine nitrogen. This in turn facilitates the intramolecular nucleophilic attack at C2 of the benzimidazole ring, leading to the formation of the active sulfenamide and sulfenic acid forms. The methyl groups at positions 3 and 5 also enhance the nucleophilic character of the unionized pyridine nitrogen through positive induction, a sigma bond effect.

The C2 position of the benzimidazole is made more electrophilic by the pi electron donating effect of the benzimidazole 5-OCH3 group, which enhances N3 protonation that in turn pulls electrons from C2 through sigma bonds. The OCH3 group does exert a negative inductive effect, but the overall impact on the benzimidazole N3 is electronic enrichment.

The rate of formation of these active uncharged (pyridine) and charged (benzimidazole) forms is directly correlated with the onset of relief from symptoms. We will see that most of the newer PPIs on the market (including esomeprazole) have a faster onset of antisecretory action than omeprazole.

The major inactivating metabolic reactions of omeprazole include benzylic hydroxylation at C5 (2C19), sulfoxidation to the sulfone (3A4), and nonenzymatic reduction to the thioether. Sulfoxidation would of course be inhibited by concomitant consumption of grapefruit juice. Esomeprazole is metabolized at a much slower rate and has a higher dependence on CYP3A4, which can conduct some of the CYP2C19-catalyzed reactions but does so at a less vigorous pace. Omeprazole and esomeprazole inhibit CYP2C19, thus inhibiting their own metabolism with chronic dosing. The AUC of these 2 PPIs increase in a nonlinear fashion over time due to slowed biotransformation and clearance.

While many hypothetical drug-drug interactions can be envisioned based on the involvement of omeprazole with CYP2C19, the only one of clinical significance is the 25%-50% inhibition of clearance of the anxiolytic diazepam (also metabolized by CYP2C19). Co-administration of diazepam and omeprazole can result in dangerously high diazepam blood levels. A serious drug-drug interaction with S-warfarin (the most active isomer of this drug) might be reasonably assumed, but fortunately co-administration of S-warfarin with omeprazole does not result in a significant increase in anticoagulation.

Omeprazole and esomeprazole must be used with caution in CYP2C19 extensive metabolizers who are taking other drugs metabolized by the CYP2C19 isoform. In this case, the dose of the CYP2C19-vulnerable drug may be higher than normal to account for the accelerated metabolism. If omeprazole or esomeprazole is co-administered, the competition for CYP2C19 (primarily a risk with omeprazole) coupled with inhibition of this enzyme (a risk with both omeprazole and esomeprazole) could lead to an inadvertent overdose of the other CYP2C19-metabolized drugs. How dangerous this would be would of course depend on the safety margin of the drugs involved.

The dose of omeprazole can be decreased in patients known to be of the "poor 2C19 metabolizing" phenotype. Since all PPIs are relatively free of adverse effects, doses do not normally need to be decreased in the elderly or in patients with renal or mild to moderate hepatic impairment. Do watch these patients closely, however, as the risk for increased plasma levels of active drug certainly

exists (this is true of all PPIs, not just omeprazole). Some advocate the use of esomeprazole or rabeprazole in the elderly due to their lower dependence on CYP-mediated metabolism.

A positive drug-drug interaction is noted when clarithromycin and any CYP3A4-vulnerable PPI are co-administered, which they often are in the "triple therapy" approach to the eradication of *H. pylori*-induced ulcers. Clarithromycin inhibits CYP3A4 (and to a lesser extent CYP2C19) and halts the formation of inactive metabolites, especially the 3A4-generated sulfone. This in turn enhances the effectiveness of the PPI in helping to eradicate the *H. pylori* organism. Remember that all proton pump inhibitors raise gastric pH, which may influence the absorption profile of other drugs (eg, Vitamin B12, theophylline, ketoconazole, etc).

As there is no asymmetric carbon atom in omeprazole some of you may be wondering about the stereochemistry of esomeprazole. Hopefully, you're also puzzling about how the basic magnesium salt of esomeprazole forms. While there is no chiral carbon in omeprazole, the sulfinyl group is not freely rotating and, as such, can be assigned an absolute configuration. So the "S" configuration is related to the orientation of the SO group. This highly electron-withdrawing group also weakens the normally neutral pyrrole N-H bond to the extent that it can actually be lost when treated with $Mg(OH)_2$ (eg, this "neutral" nitrogen has gained acidic character). As a salt, esomeprazole magnesium can be dissolved in water for short-term IV administration when oral therapy is either not feasible or inappropriate.

Since esomeprazole is metabolized at a much slower rate than racemic omeprazole, it has a slower clearance and a higher AUC. There is a lower risk of inter-patient variation as a result of CYP2C19 phenotype and it has a faster onset of action compared to omeprazole. In the 40 mg dose, its antisecretory action has been compared to 20 mg rabeprazole (the most potent PPI).

Lansoprazole (Prevacid)

Indications include active duodenal ulcer, gastric ulcer, GERD, erosive esophagitis and hypersecretory conditions. Dosage forms: disintegrating tablets, delayed release capsules, and delayed release granules for oral suspension (30 mg and 15 mg), powder for IV injection (30 mg/vial)

SAR Notes. Despite the negative inductive electronic pull of the 3 fluorine atoms of the trifluoroethoxy ether at C4 of the pyridine ring, the ether oxygen can still donate electrons through the pi system to increase the nucleophilic character of the pyridine nitrogen (in unionized form). A single methyl group assists in this effort by pushing electrons toward the pyridine nitrogen through sigma bonds. While there is no electron-donating C5 substituent on the benzimidazole ring to augment the electrophilic character of C2, the rate of formation of the reactive sulfenamide and sulfenic acid intermediates is still relatively fast.

The half-lives of omeprazole and lansoprazole at pH 1.3 are 4.7 and 3.2 minutes, respectively, and their ATPase inhibition vs. time curves under strongly acidic conditions are essentially identical. Because of their relatively high reactivity and activation rate, both lansoprazole and omeprazole react selectively with CYS813 on the proton pump. Once this disulfide bond is formed, access to CYS822 is blocked so very few molecules of this "second cysteine" are oxidized by these 2 PPIs.

Lansoprazole is metabolized predominantly by CYP2C19, but its reliance on this enzyme is somewhat less than omeprazole. Along with omeprazole, it is claimed to both competitively inhibit CYP2C19 and induce the synthesis of CYP1A isoforms, but there are no clinically significant drug-drug interactions reported in the literature for this PPI.

Pantoprazole Sodium (Protonix)

Indications include GERD, erosive esophagitis and hypersecretory conditions. Unlabeled use in the treatment of duodenal and gastric ulcers. Dosage forms: delayed release tablets (40 mg), powder for IV injection (40 mg [as base]/vial).

SAR Notes. The electron withdrawing difluoromethoxy has replaced the C5-OCH3 group found on the benzimidazole moiety of omeprazole. Along with the electron-withdrawing sulfinyl group, this makes the normally neutral imidazole NH group acidic enough for water-soluble sodium salt formation. These 2 fluorine atoms are also close enough to the oxygen atom to impact its electronic character. Despite the fact that the 4-methoxy group on the pyridine ring is trying to enhance the unionized pyridine nitrogen's nucleophilic character, the 5-difluromethoxy group on the benzimidazole has a decidedly inhibitory effect on the ability of the benzimidazole N3 to protonate.

A look back at the pKa table presented earlier in this lesson will confirm that pantoprazole has the lowest pKa2 value (0.11) of all the PPIs. This means that the benzimidazole N3 is more reluctant to take on proton compared to the other PPI structures, which have pKa2 values between 0.62 and 0.79. Since the benzimidazole N3 protonation step is essential for the activation of C2 for nucleophilic attack, the overall reactivity of pantoprazole is the lowest of all the PPIs. The half-life of pantoprazole at pH 1.3 is a whopping 9.3 minutes, documenting a much slower

conversion to the reactive sulfenic acid and sulfenamide intermediates. The much slower activation of pantoprazole compared to other PPIs means it has time to reach and inactivate CYS813 and CYS822. The CYS813-selectivity observed with omeprazole and lansoprazole has been lost.

The 2C19 pathway is most critical for pantoprazole inactivation, although CYP3A4 is also involved. No clinically relevant CYP-mediated drug-drug interactions have been noted with co-administered drugs.

Rabeprazole Sodium (Acidphex)

Indications include active duodenal ulcer, erosive GERD, and hypersecretory conditions. Unlabeled use in gastric ulcer. Dosage forms: delayed release tablets (20 mg).

SAR Notes. This PPI is the most highly reactive of those currently marketed. The pKa1 of 4.53 is the highest of any available PPI which promotes extensive protonation of the pyridine nitrogen and allows for selective accumulation in the acidic environment of the parietal cell (10X that of omeprazole). The high parietal cell concentration of rabeprazole compared to the other PPIs is certainly one factor in its superior anti-secretory activity, but it's not the whole story! Read on.

The relatively high pKa1 indicates that the nucleophilic character of the pyridine nitrogen in its unionized form will be better than we've seen with the other marketed PPIs. This high pKa1 is attributed to the electron donating effect of the methoxypropoxy substituent on the pyridine ring which provides a greater amount of pi electron push than the trifluoroethoxy substituent of lansoprazole. Even though there's a lower percentage of the pyridine nitrogen in unionized form, this is overcome by the fact that the pyridine atoms which are unionized are electronically "supercharged" and ready for the intramolecular nucleophilic attack at the benzimidazole C2 position.

In addition the pKa2 value of 0.62 provides a level of benzimidazole N3 protonation (and C2 activation) equal to that of lansoprazole. Taken together, the greatly enhanced nucleophilicity of the pyridine nitrogen coupled with a high degree of C2 activation results in the very rapid formation of the reactive sulfenic acid/sulfenamide intermediates (over 10 times faster than lansoprazole) and a very fast onset of proton-pump inhibiting action.

The activation half-life of rabeprazole in acidic media is approximately 1.3 minutes, which is the shortest of all the PPIs. In 20-mg doses, rabeprazole exhibits the highest level of gastric acid secretion control within the first 24 hours of therapy. It takes a 40-mg dose of esomeprazole to provide the same degree of relief from gastric acid-induced discomfort that is obtained from 20 mg of rabeprazole. When used in combination with amoxicillin and clarithromycin for the eradication of *H. pylori*, rabeprazole produces positive results in 7 days compared to the 10-14 day course of therapy recommended for esomeprazole and lansoprazole, respectively.

Rabeprazole has the lowest dependence of all PPIs on CYP isoforms for its biotransformation and is primarily inactivated through nonenzymatic conversion to the thioether. No CYP-mediated drug-drug interactions involving rabeprazole have been noted in the literature.

SUMMARY

Along with the antineoplastic agents, the proton pump inhibitors are the most mechanistically complex of the drug classes covered in the *Chemical Basis* courses. If intellectually equipped with a clear understanding of acid-base chemistry, functional group properties, and the basic principles governing electron movement through molecules, pharmacy students are fully able to appreciate the beauty of this mechanism and how it defines the action of these widely utilized therapeutic agents. Some might question whether pharmacy students need to understand mechanism at this detailed level, but it has been this author's experience that students find great satisfaction in their mastery of the chemical basis of drug action, and that such knowledge builds professional competence and stimulates professional pride. Providing students the opportunity to grasp the molecular mechanisms that underpin drug action helps them realize the unique contributions they can make to therapeutic decision-making and gives them the tools needed to meet their professional responsibility as the chemists of the healthcare team.

Appendix 1. Selected student responses to the question "How do you see yourself using your knowledge of drug chemistry in your future practice?"

I am already using my Med Chem knowledge as a pharmacist intern. Med Chem provides the bottom line about how drugs work, giving me the whole picture that connects patients' medical conditions and lifestyles to the best therapeutic choice. I love being able to answer patients' questions based on the structure-activity relationships I learned in class that week. Med Chem builds a strong foundation that I can build on in *Therapeutics*. It also gives me the tools I need to evaluate drugs that will hit the market in the future.

I already see myself using the knowledge I have learned in this class. I work at Walgreens and I tend to "test" myself as I am working to see what I know when patients ask questions based on things we have already

studied. I think about pharmacophores and specific DDI's that we went over–for example a patient asked if taking Prilosec OTC was okay with her Lipitor. I was like, "I KNOW THIS!"

It's not so much how the medicinal chemistry I am learning today will affect my future practice but how it's already affecting my current practice. I am sure you will receive answers on how SAR and knowing how each drug class will interact with each person can be used for optimal effects. I will also use this in my future practice, but already I have seen a dramatic change in the way I look at drugs in the pharmacy. Before when I wanted to know something about a drug or if a patient had a question I would look the information up in the drug info book and read effects and not really know why these things were happening. Now the first thing I do when questioning a drug is look at the chemical structure to get a basic idea of what to expect from a specific drug. By being able to do this I have grown exponentially in terms of my current internship since the start of the semester and I can credit most of that to this class.

I think that this class has already been exceptionally helpful for understanding patient therapy. I currently work as a technician. I am often scheduled to work as a technician in the cardiac unit. When we went through the adrenergic section I often related the drug name to the picture of the structure in my head. I was able to think about how the drug was acting on the patient based on modifications of the chemical structure. I can continually see myself using this knowledge. Knowing what chemical groups are on a compound also allows me to realize potential for DDI. Learning about medications becomes easier when you can learn about the structures.

Having an understanding of HOW exactly the drug works in the body allows me to have a better idea of allergies interactions and overall therapeutic decisions. Having this understanding of drug chemistry will allow me to help my patients understand what is going on inside of their bodies. It will help me portray a general idea of what is going on as opposed to just telling someone to take a drug and trust me that it will work.

Medicinal chemistry has made me much stronger in my chemistry background and made me a critical thinker. I can see myself looking back to concepts learned in this class and trying to figure out a clinical situation involving a patient.

Appendix 2. Proton Pump Inhibitors Learning Objectives

- Describe the receptor-based mechanisms whereby gastric acid secretion can be inhibited and compare the extent of acid secretion inhibition provided by H2 antagonists and proton pump inhibitors.
- Based on their receptor binding characteristics differentiate between the reversible inhibition of gastric acid secretion provided by the H2 antagonists and the irreversible inhibition provided by proton pump inhibitors.
- Use the Henderson-Hasselbalch equation to calculate the i/u ratio of any proton pump inhibitor functional group with acid-base character.
- Identify the importance of CYS813 and/or CYS822 of H^+, K^+-ATPase in the irreversible reaction with proton pump inhibitors.
- Describe the role of the anionic proton pump residues GLU (and possible ASP) residues in orienting proton pump inhibitors for nucleophilic attack by CYS813 (and CYS822 when allowed).
- When given the proton pump inhibitor activation pathway, describe the chemical reactions that covert these compounds from their parent (sulfinyl) form to the final sulfenic acid and sulfenamide forms that bind covalently to H^+,K^+-ATPase.
- Describe the importance of pKa1 and pKa2 on relative activation rates of proton pump inhibitors. Explain the dual (and conflicting) role of electron donating substituents at C4 of the pyridine ring in promoting potent anti-secretory action. Describe how electron donating substituents at C5 of the benzimidazole ring activate C2 for nucleophilic attack by increasing the extent protonation at N3.
- Predict and describe the metabolic pathways that inactivate each proton pump inhibitor. Name the specific enzymes that catalyze each degradative reaction identify their relative importance to the biotransformation process and draw the structure of the metabolites.
- Recognize the potential for drug-drug interactions due to proton pump inhibitor-induced achlorhydria and the potential for drug-drug interactions with co-administered CYP2C19 substrates in patients who are extensive 2C19 metabolizers.
- Identify anticipated proton pump inhibitor therapeutic outcomes based on CYP2C19 phenotype.
- Apply SAR to accurately predict the pharmacological activity profiles of marketed proton pump inhibitors.

Appendix 3. Study questions for the proton pump inhibitors lesson.

1. Why is the pKa value of each basic nitrogen atom on proton pump inhibitor structures important to pharmacological activity? What are the activity "pros and cons" of having the cationic and unionized forms of each?
2. Using Figure 2 as a guide, talk someone through the proton pump inhibitor activation pathway. Those of you who are married or in a serious relationship with a "significant other" can use this study question assignment to assess their level of devotion.
3. Explain why an extremely low concentration of the BzH^+-Pyr monocation is still sufficient to inhibit the majority of the H^+,K^+-ATPase enzymes in a parietal cell.
4. Why is the spiro intermediate that is formed during the proton pump inhibitor activation pathway so unstable?
5. Using the table of pKa values provided in this lesson and analyzing the electronic nature of functional groups on the pyridine and benzimidazole rings, rank the anticipated chemical reactivity of the marketed PPIs.
6. Explain why pantoprazole but not lansoprazole is able to form a disulfide bond with CYS822.
7. A GERD patient in the OTC section of your pharmacy is concerned about the television commercial that trashes Prilosec (omeprazole) for taking a day or more to act. In layman's terms give her an explanation for the delayed onset of proton pump inhibitors and on the different therapeutic indications for products like *Tums* (calcium carbonate), *Pepcid-AC* (an H_2 antagonist), and *Prilosec OTC*.
8. What therapeutic issues might be anticipated when PPIs are administered:
   a. to patients of the "poor 2C19 metabolizer" phenotype?
   b. to patients of the "extensive 2C19 metabolizer" phenotype?
   c. with clarithromycin in the treatment of *H. pylori*-induced ulcer?
   d. with vitamin B12 supplements?
   e. with grapefruit juice?
9. What metabolic reactions are common to all PPI structures?
10. Explain why the pyrrole-type nitrogen of the benzimidazole ring (normally a neutral nitrogen) is able to relinquish proton when treated with strong bases like NaOH and $Mg(OH)_2$.

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